

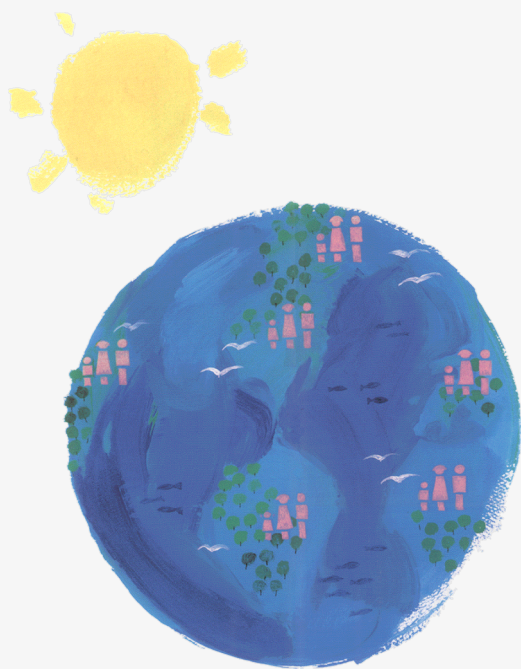
NICEATM

*National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods*

ICCVAM

*Interagency Coordinating Committee on
the Validation of Alternative Methods*

ICCVAM and NICEATM Update



William Stokes, DVM, DACLAM
RADM, U.S. Public Health Service
Director, NICEATM
Executive Director, ICCVAM

7th Meeting of the Scientific Advisory Committee on
Alternative Toxicological Methods
Bethesda, MD
June 12, 2007



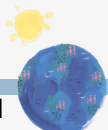
Outline

■ Updates

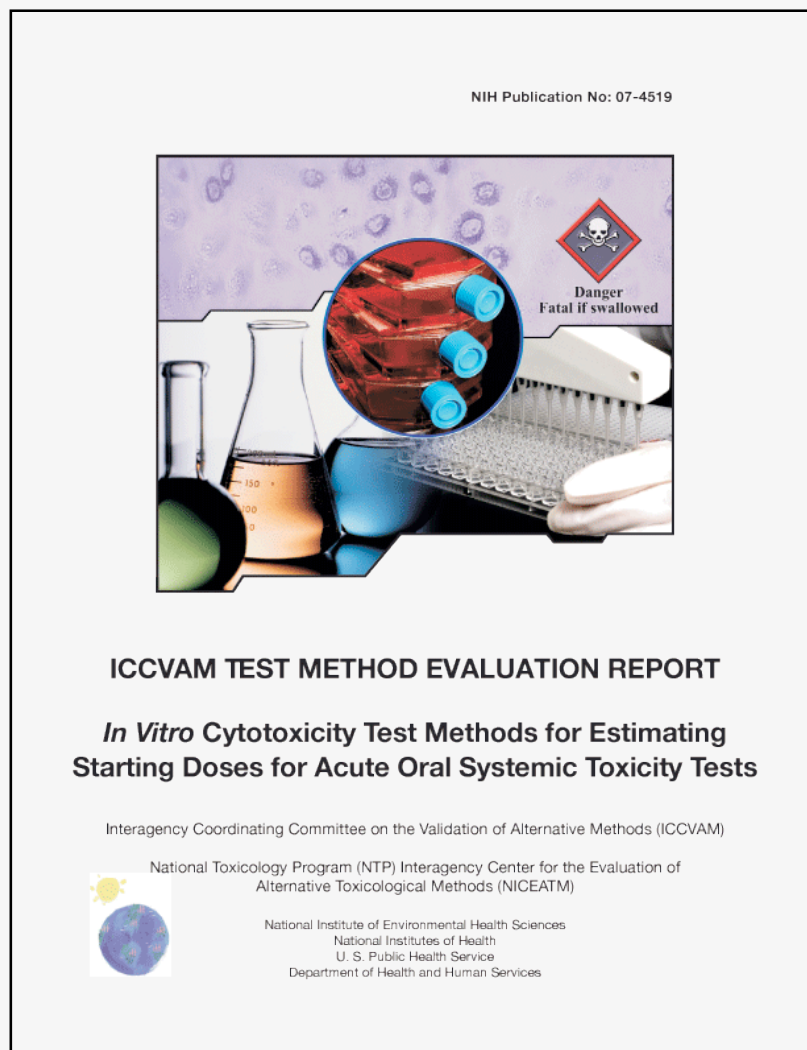
- Acute Systemic Toxicity
- Ocular Toxicity
- Biologics
- Endocrine Disruptors
- Pyrogenicity
- Immunotoxicity
- Dermal Toxicity
- Genetic Toxicity
- Outreach

■ Separate agenda items

- NICEATM-ICCVAM 5-year Plan
- *In Vitro* Pyrogen Tests
- Nominations
- NTP High Throughput Screening Initiative



Acute Systemic Toxicity: Cytotoxicity Methods

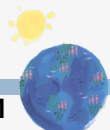


- Test Method Evaluation Report and BRD published
- Test Recommendations
 - Uses: Consider before animal testing and use where appropriate
 - Limitations
 - Protocols
 - Performance Standards
 - Future Studies
- Impact: the most commonly performed product safety test
 - Reduction: up to 50% per study
 - Refinement

<http://iccvam.niehs.nih.gov/methods/acutetox/acutetox.htm>

Acute Systemic Toxicity: ICCVAM-NICEATM Planned Activities

1. Stimulate Industry submission of comparative *in vitro* and *in vivo* data
2. Evaluate *in vitro* methods for mixtures
3. Convene international workshop
 - *In vivo* biomarkers to support development of predictive *in vitro* systems
 - Earlier more humane endpoints
 - Promising *in vitro* methods for predictive test battery
4. Identify existing *in vivo* reference data
5. Evaluate *in silico* approaches
6. Evaluate HTS cytotoxicity data on 1408 chemicals



Ocular Toxicity: *In Vitro* Test Methods for Identifying Severe and Irreversible Damage

NIH Publication No: 07-4517



ICCVAM TEST METHOD EVALUATION REPORT

In Vitro Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)



National Institute of Environmental Health Sciences
National Institutes of Health
U. S. Public Health Service
Department of Health and Human Services

- Test Method Evaluation Report published
- ICCVAM Test Recommendations
 - Uses: Consider before animal testing and use where appropriate
 - Limitations
 - Protocols
 - Validation reference chemicals
 - Future studies
- Impact: one of the top 6 most commonly performed product safety tests
 - Partial replacement
 - Refinement



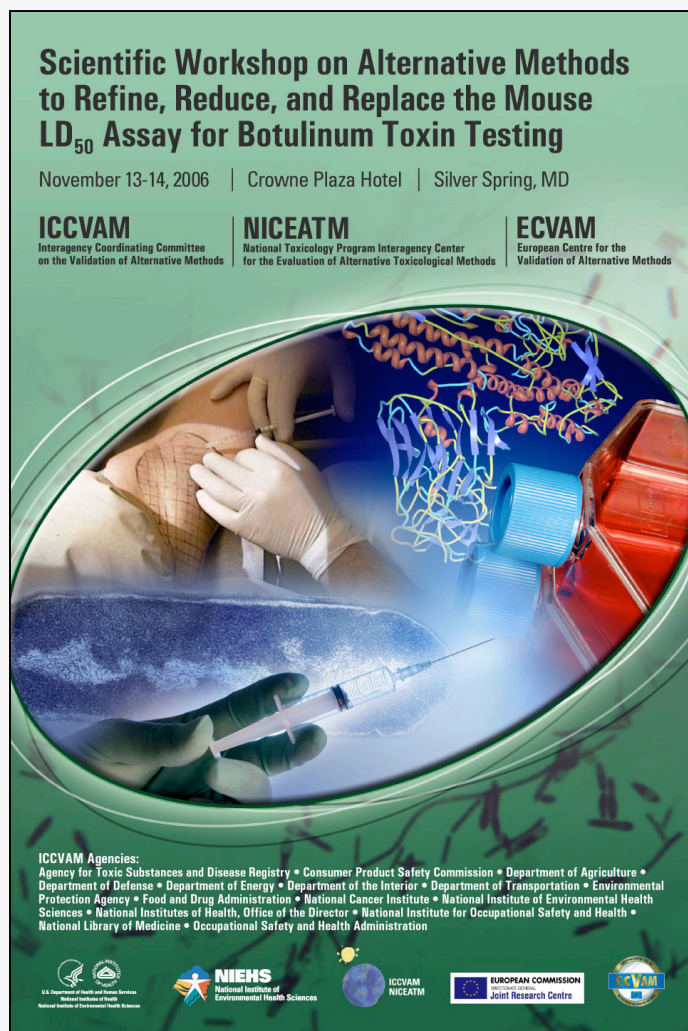
Ocular Toxicity:

ICCVAM-NICEATM Planned Activities

- Evaluate holder that maintains normal corneal curvature (BCOP)
- Develop guidance for histopathology (BCOP, IRE, ICE, rabbit)
- Encourage industry use and data submission to expand current validation databases
- Review routine use of topical anesthetics and systemic analgesics
 - *Federal Register* Notice Request for data: 72FR26396 (May 9, 2007)



Scientific Workshop on Alternative Methods for Botulinum Toxin Testing



- November 13-14, 2006
 - ICCVAM, NICEATM, ECVAM
 - Silver Spring, MD, USA
- Purpose
 - Review state-of-the-science and current knowledge of 3Rs alternatives
 - Identify priorities for research, development, and validation to advance the use of alternative methods
- Presentations on website
- Workshop Report on website
- <http://iccvam.niehs.nih.gov/methods/biologics/biologics.htm>

Endocrine Disruptor Test Methods: International Validation Study

- Stably-Transfected ER Transcriptional Agonist and Antagonist Protocols
 - Standardized LUMI-CELL[®] ER assay (XDS, Inc.)
- International independent validation study initiated
 - First NICEATM-JaCVAM-ECVAM joint study
 - U.S. and Japan labs began in April
 - ECVAM will conduct validation study “in house”

<http://iccvam.niehs.nih.gov/methods/endocrine/endocrine.htm>



Endocrine Disruptor Test Methods: OECD Test Guideline Development

1. Rat Uterotrophic Bioassay

- Extensive comments on validation status and protocol issues provided to US National Coordinator (2006-2007)
 - Recommended guidance document until evidence of adequate validation, but test guideline endorsed by NCs

2. Rat Hershberger Bioassay

- Comments provided to US NC (May 2007)




Pyrogenicity Test Methods: ICCVAM Independent Peer Panel Review Meeting

Independent Scientific Peer Review: Five *In Vitro* Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products

February 6, 2007 | Natcher Conference Center | NIH Campus
8:30 a.m. - 5:00 p.m. | Conference Rooms E1/E2 | Bethesda, MD

ICCVAM
Interagency Coordinating Committee
on the Validation of Alternative Methods

NICEATM
National Toxicology Program Interagency Center
for the Evaluation of Alternative Toxicological Methods



IL-1 β **IL-6**

ICCVAM Agencies:
Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture •
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation • Environmental
Protection Agency • Food and Drug Administration • National Cancer Institute • National Institute of Environmental Health
Sciences • National Institutes of Health, Office of the Director • National Institute for Occupational Safety and Health •
National Library of Medicine • Occupational Safety and Health Administration

NIHNS
National Institute of
Environmental Health Sciences

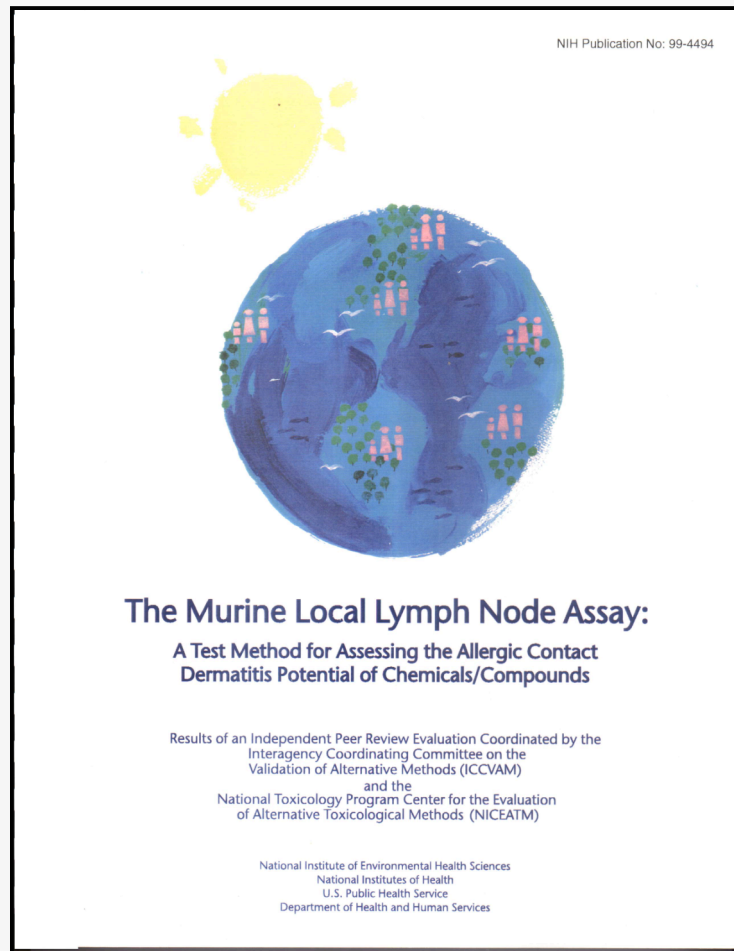
NTP
National Toxicology Program
U.S. Department of Health and Human Services

ICCVAM
NICEATM

- February 6, 2007
 - NIH, Bethesda, MD
- Expert Scientific Panel
 - 13 scientists
 - 5 countries
- Upcoming agenda item:
 - Dr. Richard McFarland, ICCVAM PWG Chair
 - Dr. Karen Brown, PRP Chair
- <http://iccvam.niehs.nih.gov/methods/pyrogen/pyrogen.htm>



LLNA: An Alternative Test Method for Allergic Contact Dermatitis Testing



- ICCVAM evaluation: 1998
 - Regulatory Acceptance: 1999
 - Implementation Workshop: 2000
 - OECD TG: 2001
- *Valid substitute for the guinea pig tests for most testing situations for allergic contact dermatitis*
- **Impact: one of the 6 most commonly performed product safety tests**
 - **Eliminates pain and distress; uses fewer animals**

<http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm>

ICCVAM Evaluation of LLNA Revisions and Issues

- Sep 2006 IWG reactivated to review new issues and LLNA revisions
- Jan 07 Nomination received from CPSC
(Discussed today as separate agenda item)
- May 07 *FR* notice (72FR27815) requesting:
- Comments on nomination
 - Data for nominated activities
 - Nominations for possible Expert Panel meeting
- Jun 07 SACATM Meeting
- Comment on priority for LLNA activities



Genetic Toxicity Test Methods: Recent Activities

■ **Draft OECD TG 487: *In Vitro* Micronucleus Assay**

- ICCVAM comments submitted to OECD via US NC
- OECD to establish an “In Vitro Micronucleus ad hoc Expert Group” to revise the draft TG

■ **Draft OECD Detailed Review Paper (DRP) 31: Cell Transformation Assays**

- ICCVAM comments to US OECD NC: Defer DRP finalization to allow incorporation of current validation study results

■ **JaCVAM *In Vivo* Comet Assay Validation Study**

- GTWG comments provided on draft protocols and study design



Dermal Toxicity: ICCVAM Evaluation of *In Vitro* Skin Irritation Test Methods

- EpiDerm™ and EPISKIN™ skin irritation assays
 - ECVAM Validation Study, 2006; ESAC recommendations, 2007
 - Evaluated for EU hazard classification scheme
- ICCVAM evaluation
 - Initiate when ECVAM validation data/report available
 - U.S./ international hazard classification schemes
- Related ICCVAM Study Plan:
 - Determine how *in vitro* dermal irritation test method will classify false negative chemicals from *in vitro* corrosivity test methods
 - Currently false negatives *in vitro* corrosivity assays: 12% to 21%
 - Confirm extent that identifying substances that directly reduce MTT (i.e., act as false negatives) will reduce false negative corrosive results

<http://iccvam.niehs.nih.gov/methods/dermal/dermal.htm>



NICEATM-ICCVAM Five-Year Plan

The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) announce a

Town Meeting

To receive public comments on a draft NICEATM/ICCVAM Five-Year Plan developed in partnership with relevant agencies to:

- Research, develop, translate, and validate new and revised non-animal and other alternative assays for integration of relevant and reliable methods into federal agency testing programs, and
- Identify areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the replacement, reduction, and refinement (reduced pain and distress) of animal tests, when this is scientifically valid and appropriate

Monday, June 11, 2007 1:00 P.M. to 5:00 P.M.

National Institutes of Health
William H. Natcher Conference Center Conference Room E
Bethesda, Maryland

For more information, please contact NICEATM:

Phone: 919-541-2384

Email: niceatm@niehs.nih.gov

Website: iccvam.niehs.nih.gov

The draft NICEATM/ICCVAM Five-Year Plan will be available on the NICEATM/ICCVAM website in May 2007

ICCVAM Agencies: Consumer Product Safety Commission, Dept. of Agriculture, Dept. of Defense, Dept. of Energy, Food and Drug Administration, National Cancer Institute, Dept. of Transportation, National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, NIH Office of the Director, National Library of Medicine, Department of the Interior, Occupational Safety and Health Admin., Environmental Protection Agency

(Logos will go here: NTP, NIEHS, HHS, NIH)

- Draft plan available May 7, 2007 on NICEATM-ICCVAM website
 - Public and stakeholder comments welcome
- June 11 public Town Meeting
- June 12 SACATM discussion and comments
 - agenda item today
- <http://iccvam.niehs.nih.gov/meetings/5yPlanTM/townmtg.htm>



ICCVAM-NICEATM Outreach Activities

■ Objectives

- Promote awareness of alternative methods
- Provide education on test method uses

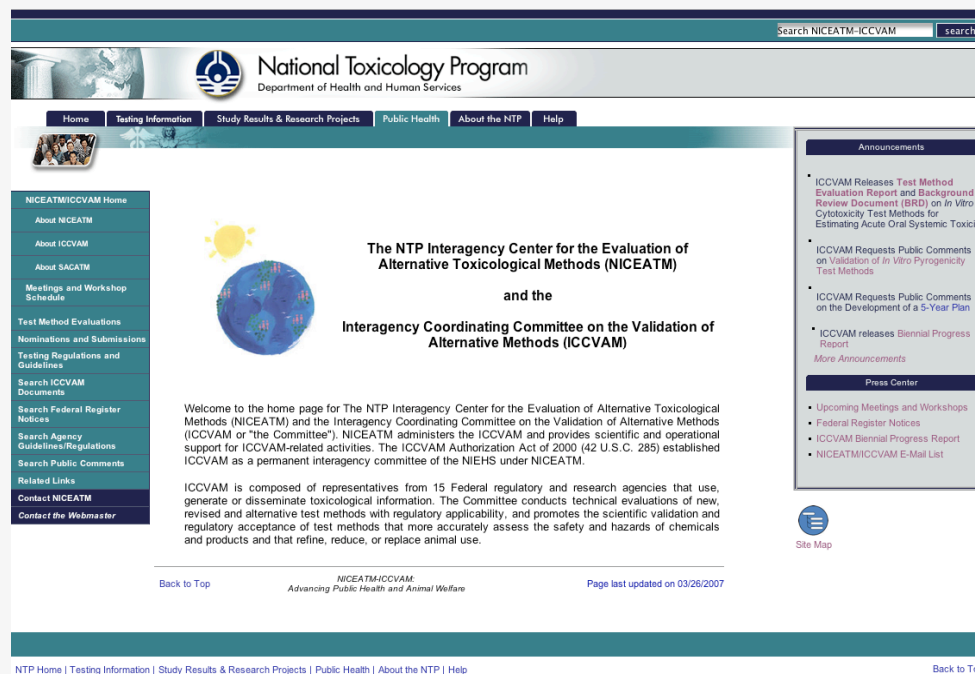
■ Society of Toxicology: March 2007 - Charlotte, NC

- 12 posters and 1 workshop presentation
 - Available on NICEATM-ICCVAM website
- ICCVAM-NICEATM brochures
- Town Meeting flyers

■ 6th World Congress on Alternatives and Animal Use in the Life Sciences: August 2007 - Tokyo, Japan

- 21 abstracts: 13 posters and 8 presentations

Enhanced Communication: Updated NICEATM-ICCVAM Website



- All NICEATM and ICCVAM publications
- Federal and international regulatory documents
- Federal Register notices
- Public comments

<http://.iccvam.niehs.nih.gov>



NICEATM-ICCVAM Progress

- Over 150 test methods evaluated since 1997
- Impact
 - Alternative methods recommended and/or adopted internationally for four of the 6 most common product safety tests
 - Recommendations to advance alternative methods
 - research, development, translation, and validation activities
 - Performance standards to expedite validation studies and regulatory acceptance
- Guidance for validation and regulatory acceptance of new, revised, and alternative methods

**ICCVAM-NICEATM 10-year Anniversary Symposium
(to be announced)**



Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Agency for Toxic Substances and Disease Registry

- Moiz Mumtaz, Ph.D.

Consumer Product Safety Commission

- Marilyn L. Wind, Ph.D. (Chair)
- * Patricia Bittner, M.S.
- * Kristina Hatlelid, Ph.D.

Department of Agriculture

- Jodie Kulpa-Eddy, D.V.M. (Vice Chair)
- ◊ Elizabeth Goldentyer, D.V.M.

Department of Defense

- Robert E. Foster, Ph.D.
- ◊ Patty Decot
- * Harry Salem, Ph.D.

Department of Energy

- Michael Kuperberg, Ph.D.
- ◊ Marvin Stodolsky, Ph.D.

Department of the Interior

- Barnett A. Rattner, Ph.D.
- ◊ Sarah Gerould, Ph.D.

Department of Transportation

- George Cushmac, Ph.D.
- ◊ Steve Hwang, Ph.D.

- Principal Agency Representative
- ◊ Alternate Principal Agency Representative
- * Other Designated Agency Representatives

Environmental Protection Agency

Office of Science Coordination and Policy

- Karen Hamernik, Ph.D.
- Office of Research and Development**
- ◊ Julian Preston, Ph.D.
- * Suzanne McMaster, Ph.D.
- OECD Test Guidelines Program**
- * Jerry Smrchek, Ph.D.
- Office of Pesticides Programs**
- * Amy Rispin, Ph.D.
- * Deborah McCall

Food and Drug Administration

Office of Science and Health Coordination

- Suzanne Fitzpatrick, Ph.D., D.A.B.T.
- Center for Drug Evaluation and Research**

- * Abigail C. Jacobs, Ph.D.

Center for Devices and Radiological Health

- * Melvin E. Stratmeyer, Ph.D.

Center for Biologics Evaluation and Research

- * Richard McFarland, Ph.D., M.D.
- * Ying Huang, Ph.D.

Center for Food Safety and Nutrition

- * David G. Hattan, Ph.D.
- * Robert L. Bronaugh, Ph.D.

Center for Veterinary Medicine

- * Devaraya Jagannath, Ph.D.
- * M. Cecilia Aguila, D.V.M.

National Center for Toxicological Research

- * William T. Allaben, Ph.D.
- Paul Howard, Ph.D.
- Office of Regulatory Affairs**
- * Lawrence A. D'Hoostelaere, Ph.D.

National Cancer Institute

- Alan Poland, M.D.
- ◊ T. Kevin Howcroft, Ph.D.

National Institute of Environmental Health Sciences

- William S. Stokes, D.V.M., D.A.C.L.A.M.
- ◊ John R. Bucher, Ph.D., D.A.B.T.
- * Rajendra S. Chhabra, Ph.D., D.A.B.T.
- * Jerrold J. Heindel, Ph.D.
- Raymond Tice, Ph.D.

National Institute for Occupational Safety and Health

- Paul Nicolaysen, V.M.D.
- ◊ K. Murali Rao, MD, Ph.D.

National Institutes of Health

- Margaret D. Snyder, Ph.D.

National Library of Medicine

- Vera Hudson, M.S.
- ◊ Jeanne Goshorn, M.S.

Occupational Safety and Health Administration

- Surender Ahir, Ph.D.



NICEATM

■ NIEHS

- | | |
|-------------------------------------|--|
| – William S. Stokes, D.V.M., DACLAM | Director; Project Officer |
| – Raymond Tice, Ph.D. | Deputy Director |
| – Debbie McCarley | Special Assistant; Asst. Project Officer |

■ NICEATM Support Contract (ILS, Inc.)

- | | |
|----------------------|------------------------|
| – David Allen, Ph.D. | Principal Investigator |
| – Doug Winters, M.S. | Project Manager |

